REMARKS

Applicants and the undersigned reviewed the Office Action carefully before preparing this response. Reconsideration is respectfully requested with regard to claims 1-17. Nonetheless, in light of the positions presented herein, all claims are believed to be in condition for allowance.

The Examiner raised several issues with regard to the numerous amino acid sequences provided in the specification. The Examiner's concerns are well-taken, particularly as it appears that identifiers were inadvertently not provided for the sequences of Figures 7A and 7B. An amendment to Claim 28, the specification and the written sequence listing, also in computer readable format, accompanies this response. Likewise, the specification has been reviewed thoroughly for additional identifier omissions or sequence inconsistencies.

In particular, with regard to identifiers, the Examiner objected to claims 28-29 for reasons relating to the sequence rules. Claim 28 is hereby amended to recite more specifically the corresponding sequence identifier number. Accordingly, claims 28-29 are believed to be in condition for allowance, a status previously afforded claims 30-31 and one Applicants gratefully acknowledge.

The Examiner rejected numerous claims under 35 U.S.C. § 112, second paragraph, as indefinite. Again, the Examiner's concerns are well-taken, as indicated by amendments to claims 3, 4, 6 and 14-16. Such amendments are presented merely for purposes of clarification, without further limitation. The subject claims and those dependent therefrom are now believed to be in condition for allowance.

Claims 1-17 were rejected under 35 U.S.C. § 112, first paragraph, as non-enabling, for a spreading agent comprising at least one N-substituted glycine monomer for a corresponding mimic of surfactant protein B. Applicants

respectfully disagree. The Examiner is reminded that the law does not require a specification to be a blueprint or a production specification to satisfy the enablement requirement. Rather, it has been long-held that a specification need not describe—and best omits—that which is well-known in the art. The full range of subject matter of claims 1-17 is adequate described in the specification, as would be understood by those skilled in the art.

Applicants appreciate the Examiner's acknowledgement that the specification is enabling for the inventive mimics of surfactant protein C (SP-C), but respectfully disagree that undue experimentation is required to support the scope of independent claims 1 and 9. As shown below, the naturally occurring surfactant proteins have been thoroughly characterized both by way of structure and function. Incorporation of N-substituted glycine monomers to achieve, for instance with SP-B mimics, comparable structural and functional effects is not complex, but a straightforward exercise given the enabling disclosure for SP-C mimics. Additional experimentation is expected with any invention. Even considerable experimentation over an extended period of time is permissible, where as here the specification would guide one skilled in the art how that experimentation should proceed.

As mentioned above, the Examiner concedes the present specification is enabling over the range of SP-C mimics contemplated herein. Such compounds can be prepared as known in the art. Literally, hundreds of peptoid amine reactants are commercially-available, for optional use with amino acids, to provide a great diversity of peptoid-peptide chimerae or completely peptoid-based SP-C mimics (see, specification pages 17-18 and Examples 1-2). Simple choice of reactants and routine cycle repetition, using an automated peptide synthesizer, provide peptoid-peptide chimerae or peptoid mimics of virtually any sequence desired and up to about 50-60 monomers in length. Structurally, such compounds are of a length sufficient to contact or functionally interact with a lipid bilayer, and have as known

in the art a helical secondary structure comparable to natural polypeptides. (See, specification pages 17-19.) Helical structure is readily evidenced by circular dichroism (CD) spectroscopy. (See, i.e., Examples 2 and 8, and Figure 8.) The activity of such compounds is indicated by measurement of Langmuir-Wilhelmy surface balance (LWSB) surface pressure-area isotherms and dynamic surface tension (via pulsating bubble surfactometry), using known techniques, and shown to be comparable to the natural polypeptides. (See, Examples 3-5 and 9-11.)

Likewise, much is known in the art regarding surfactant protein SP-B, a small, predominantly helical protein believed to exist in vivo as a dimer of two 79-amino acid proteins, each with multiple internal disulfide bonds. While the natural protein has a complicated structure, it has been shown that its biophysical functioning in a lipid film can be closely mimicked using only the protein fragment SP-B 1-25 (the first 25 amino acid residues of the amino-terminal region) [A. Waring, W. Taeusch, R. Bruni, J. Amirkhanian, B. Fan, R. Stevens, J. Young, "Synthetic amphipahtic sequences of surfactant protein-B mimic several physiochemical and in vivo properties of native pulmonary surfactant proteins," Peptide Research, 2: 308-313, 1989](see page 311, Table 2). Moreover, residues 1-25 of SP-B have been shown to be helical and amphipathic in structure [L.M. Gordon, K.Y.C. Lee, M.M. Lipp, J.A. Zasadzinski, F.J. Walther, M.A. Sherman, A.J. Waring, "Conformational mapping of the N-terminal segment of surfactant protein B in lipid using ^{13}C-enhanced Fourier transform infrared spectroscopy," J. Peptide Research 55: 330-347, 2000](see page 340, paragraph 2, sentence 2).

Hence, there is a simple, relatively short residue fragment of SP-B, of known sequence and secondary structure, which works well as a surface-active agent (spreading) and additive to surfactant lipids, and which is known to improve lung function in animals with respiratory distress [A. Waring, W. Taeusch, R. Bruni, J. Amirkhanian, B. Fan, R. Stevens, J. Young, "Synthetic amphipahtic sequences of

surfactant protein-B mimic several physiochemical and in vivo properties of native pulmonary surfactant proteins," Peptide Research, 2: 308-313, 1989](see page 311, paragraph 5, sentence 5).

Furthermore, as with SP-C, the known amphipathic structure of SP-B 1-25 dictates that the mimic should have a helical structure in solution. In SP-C, there is one cationic face to the helix, and the rest of the helical circumference carries predominantly hydrophobic side chains. It has been shown in the literature, in an unrelated context, that it is a simple task to design an oligopeptoid molecule having a stable helical structure, amphipathic with one presentation of one cationic face of the helix, via a 3-fold patterning of cationic residues such as NLys (N-substituted butylamine moiety) in the peptoid sequence. In particular, helical oligopeptoids with these types of sequence and structural features have been reported. [K. Kirshenbaum, A.E. Barron, R.E. Goldsmith, P. Armand, E.K. Bradley, K.T.V. Truong, K.A. Dill, F.E. Cohen, R.N. Zuckermann, Sequence-specific polypeptoids: A diverse family of heteropolymers with stable secondary structure, Proc. Natl. Acad. Sci. USA (1998) 95, 4303-4308] (see page 4305, Table 2 and Figure 2, peptoids 2 and 3). For instance, in this publication, it was shown that the inclusion of the N-substituted S-N-1-phenylethyl side chain (Nspe) as the hydrophobic moiety, as either 1/3 or 2/3 of the peptoid sequence, patterned in a repetitive way with 3-fold periodicity, yielded a peptoid with an overall helical structure as reported by circular dichroism spectroscopy. As shown in another publication, the structure of the peptoid helix with Nspe side chains is such that the helix has 3 residues per turn.

Accordingly, the design of a simple sequence of residues to mimic SP-B would be understood by one skilled in the art—given Applicants' work with SP-C mimics. Known techniques can be used to prepare an oligomer with an overall helical structure and amphipathic properties where one "face" of the helix carries a

net cationic charge. Moreover, it is a routine exercise for one skilled in the art to create a sequence-specific peptoid oligomer having a helical structure and a cationic face to the peptoid helix via inclusion of the NLys monomer or other cationic monomers such as Narg (as described in the application). It is demonstrated in the application that peptoid analogs of SP-C, which capture the amphipathic sequence patterning and helical structure of the natural protein, very closely mimic the biophysical functioning of natural SP-C. Therefore, it would be reasonably expected by one in the art that peptoid analogs of residues 1-25 of SP-B would also mimic natural SP-B and provide comparable activity.

Indeed, since filing the present application, it has been shown experimentally that mimics of SP-B, using oligopeptoids under the aforementioned sequence and structural considerations, provide functional effects comparable to both natural SP-B and the SP-C mimics illustrated in the application.

By declaration of Annelise E. Barron, recent experimental results are provided in a manuscript soon to be submitted for publication in *Chemistry and Biology*. As described therein, using synthetic procedures in the application, peptoid mimics of residues 1-25 of SP-B were prepared as easily as the SP-C mimics, demonstrating a corresponding diversity of sequence and length. Consistent with previously synthesized SP-C mimics, and as would be understood in light of the aforementioned art, the SP-B mimics were shown to have an overall helical secondary structure, with requisite hydrophobicity and a cationic face. Useful peptoid length was readily determined given known residue dimension. Just as with the SP-C mimics, helicity of the SP-B analogs was confirmed using CD spectroscopy. Likewise, surface activity was confirmed using techniques demonstrated in the application. Overall, the results showed the SP-B mimics described in the application have activities and provide functional effects comparable to both natural SP-B and mimics of SP-C.

In light of the foregoing, Applicants respectfully disagree with the Examiner's assessment under § 112, first paragraph. The present specification is enabling for a wide range of SP-B mimics. Even though natural SP-B is complex, the functionally-pertinent residues comprise a minor segment of the dimer compound. Given known techniques to provide helical length and dimension, preparation of the SP-B mimics was a straight-forward extension of the synthetic technique described for the SP-C mimics. Routine measurement of surface pressure-area isotherms and dynamic surface tensions, as understood by those in the art, quickly confirms activities predicted by the aforementioned structural relationships.

Accordingly, the specification enables preparation of both SP-B and SP-C peptoid mimics having function indicative of alveolar surface activity. The § 112, first paragraph, rejection should be withdrawn, with claims 1-17 allowed to proceed toward issue.

As noted above, independent claim 28 is also believed to be in condition for allowance, with the appropriate sequence identifier. As a matter of technical clarification, the term NX_3 is now recited as a peptoid monomer, as the polypeptoid nature of the spreading agent is inherent with n as an integer greater than 1. A similar clarification is provided in claim 30. If agreeable with the Examiner, the term "monomer" might also be used elsewhere throughout the claims to more correctly and technically distinguish amino acid residues from their replacement with N-substituted glycine monomers.

This application is now believed to be in condition for allowance. Action consistent therewith is respectfully requested. The Examiner is invited to contact the undersigned by telephone should any issue remain. Thank you for your time and consideration.

Respectfully submitted,

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